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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 10/698,238 | 10/31/2003 | Min Wan | 2000.615 USD1 | 2367 |

27624 7590 05/07/2007
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| EXAMINER |
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LUKTON, DAVID

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| ART UNIT | PAPER NUMBER |
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1654

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| MAIL DATE | DELIVERY MODE |
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05/07/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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|------------------------------|--------------------------------------|-----------------------------------|--|
| Office Action Summary | Application No. 10/698,238 | Applicant(s) WAN ET AL. | |
| | Examiner David Lukton | Art Unit 1654 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 February 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 24-39 is/are pending in the application.
- 4a) Of the above claim(s) 32 and 37-39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 24-31 and 33-36 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Pursuant to the directives of the response filed 2/28/07, claims 35 and 39 have been amended. Claims 24-39 remain pending.

Applicants have requested clarification as to whether or not the examiner is maintaining the "election-of-species" requirement. In response, the examiner is indeed maintaining the requirement, and may withdraw claims, as appropriate, which do not encompass the elected species/subgenera. The examiner also acknowledges that applicants have traversed the election requirement, and that applicants will ultimately have the right to petition the requirement.

Claim 32 is withdrawn from consideration, since the elected method is such that the proteins are not purified. Claims 37-39 are also withdrawn. If one starts with a cell lysate that contains DNA, proteins, endotoxins and other cellular constituents, and carries out a process which produces a protein with purity in excess of 95%, by almost any standard one is effecting a protein purification. In the response filed 6/16/06, applicants elected a process in which the proteins that were present in the initial cell lysate were not purified. It is noted that applicants asserted that claims 37-39, as presented at the time of the election requirement, encompassed the elected process, despite the fact that the elected process excluded a step of purifying proteins. There was actually justification for applicants' assertion that claims 37-39, as presented at the time of the election requirement, fell within

the scope of the elected invention. The reason is that claims 37-39, at that time, made reference to the yield of the protein solution, rather than to the yield of the protein. As such, recitation of a yield was entirely meaningless, as it pertained to a volume of a solution, without regard to the content of that solution. Now that claims 37-39 have been amended to make reference to the protein itself (rather than the solution), there is no way to argue that a process which produces proteins with a purity in excess of 95% is not a protein purification (especially considering the high levels of impurities that were initially present). Accordingly, claims 37-39 do not encompass the elected invention.

Applicants' arguments filed 2/28/07 have been considered and found persuasive in part. The rejection of claims 24-32 and 37-39 as unpatentable over Hsu ('328) in view of Bobbitt ('967) further in view of Hennen ('534) or Colpan ('371) is withdrawn. Claims 24-31 and 33-36 are examined in this Office action.



Claims 24-25 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of USP 6,995,246. Although the conflicting claims are not identical, they are not patentably distinct from each other; there is overlap of the claimed subject matter. Claim 1 of the patent is subgeneric to claim 24 of the instant application. Since the respective disclosures are the same, it would have been obvious to the protein chemist (or molecular biologist) of ordinary skill, or even the patent

attorney of ordinary skill that claim 24 encompasses the use of polyethyleneimine.



Claims 24-25 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 24 of copending application Serial No. 10/698230. Although the conflicting claims are not identical, they are not patentably distinct from each other. There is overlap of the respective genera. Applicants are requested to offer some reason as to why they believe there is no overlap.

[This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented].

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d)



Claims 24-31 and 33-36 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to a method of removing suspended particles from a solution. However, given the meaning of the term "solution", this would appear not to be possible. Consider the following hypothetical claims:

100. A method of removing water from an anhydrous solution comprising

101. A method of removing sodium chloride from distilled water comprising

102. A method of removing particles from a liquid mixture, wherein all components are dissolved in the liquid, and as such there are no particles to remove.

Each of the foregoing claims (100-101) represent examples that are analogous to the present claims. If one has a vial that contains a “solution”, that vial does not contain a suspension. Similarly, if one has a vial that contains a suspension, that vial does not contain a solution. Thus, claim 24 represents a contradiction in terms. If it is really true that one has a “solution” that contains soluble proteins and DNA, then that solution cannot contain particles. Of course, a composition can contain particles, as would a suspension or a mixture or a cell lysate. But as matters currently stand, the claims are indefinite.



The following is a quotation of 35 USC. §103 which forms the basis for all obviousness rejections set forth in the Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 24-31 and 33-36 are rejected under 35 U.S.C. §103 as being unpatentable over Hsu (USP 6,008,328) in view of Hennen (USP 6,468,534) or Colpan (USP 6,274,371).

As indicated previously, Hsu discloses a method for obtaining KGF from lysed bacteria which expressed the KGF. Cell lysis is also disclosed (e.g., col 11, line 10+). Hsu also discloses (col 12, line 25+) removal of endotoxins. Also disclosed (col 11, line 19) is the use of a "filter aid" to clarify the cell lysate. Also disclosed (e.g., col 2, line 56+) is blocking of cysteine sulfhydryl groups. Hennen discloses (col 10, line 41) that diatomaceous earth is useful for preventing clogging of filters when filtering protein solutions that contain precipitates. Hennen does not disclose a method which comprises removing suspended particles from a lysate, and which method also comprises reducing the amount of DNA and endotoxins. Colpan discloses a method for removal of cellular debris comprising a filtration step. A preferred filtration aid (col 2, line 31+) is diatomaceous earth. Colpan does not disclose a method which comprises removing suspended particles from a lysate, and which method also comprises reducing the amount of DNA and endotoxins. Thus, a practitioner of the Hsu invention would purify KGF from lysed bacteria by using various methods including a filtration aid. Hsu discloses

the claimed invention, except that there is no specific teaching that the "filter aid" should be diatomaceous earth. However, a protein chemist in possession of Colpan or Hennan would have recognized that if a filter aid is used, diatomaceous earth would have been effective for this purpose.

In response, applicants have argued that the references do not recite the phrase "highly purified" diatomaceous earth. However, the claims impose no limitations on what this might mean. In any case, most commercial suppliers of the product would provide the diatomaceous earth with sufficient purity to qualify.

Thus, the claims are rendered obvious.



Claims 24-31, 34, 36 are rejected under 35 U.S.C. §103 as being unpatentable over Lander (US 2001/44136).

Lander discloses a method of purifying plasmid DNA that includes the use of diatomaceous earth to clarify cell lysates. In addition, Lander is replete with references to diatomaceous earth for removal of debris from cell lysates. In addition, proteins are mentioned in table 4 (page 14) and also at least one time in each of the following paragraph numbers: 11, 39, 40, 46, 48, 66, 67, 70, 71, 73, 83 and 98.

The instant claims are not drawn to a method of purifying a protein. Instead, the instant claims are drawn to a method of removing particles from a solution that contains

DNA and protein. As such, the instant claims would encompass a method, the ultimate objective of which is isolation of any cellular constituent including plasmid DNA, genomic DNA, RNA, proteins or lipids.

Consider next claim 28. The objective of Lander is to eliminate genomic DNA. Accordingly, one would have expected total DNA (genomic + plasmid) to be reduced by 100-fold.

Thus, the claims are rendered obvious.



Claim 24 is rejected under 35 U.S.C. §103 as being unpatentable over Theodossiou, I. (*Bioprocess Engineering* 16(3), 175-183, 1997) in view of Luo (USP 6,365,147) or Marquet (USP 5,561,064).

Theodossiou is focused on the use of diatomaceous earth as a filtration aid in the recovery of plasmid DNA from cell lysates. Although the emphasis is on isolation of plasmid DNA, the reference also discloses (e.g., table 5, page 182) that protein is present after the filtration. Theodossiou also discloses that some loss of DNA occurred as a result of the filtration. Theodossiou does not disclose removal of endotoxins.

Luo discloses (e.g., col 4, line 7) the desirability of, and methods for removal of endotoxins from plasmid DNA. Luo does not discuss the use of diatomaceous earth to clarify cell lysates. Marquet ('064) discloses (e.g., col 5, line 25+) the desirability of,

and methods for removal of endotoxins from plasmid DNA. Marquet ('064) does mention the use of diatomaceous earth to clarify cell lysates, but does not provide an extensive discussion of this subject.

Theodossiou meets all of the limitations of claim 24, except for the requirement that endotoxins be removed. The secondary references teach the artisan of ordinary skill how to remove endotoxins. Thus, it would have been obvious to one of ordinary skill to follow the process described by Theodossiou, and then to remove endotoxins from the plasmid DNA.



Claim 24 is rejected under 35 U.S.C. §103 as being unpatentable over Colpan (USP 6,274,371) in view of Theodossiou, I. (*Bioprocess Engineering* 16(3), 175-183, 1997).

Colpan discloses a method for isolating DNA from cell culture, such as a bacterial cell culture (e.g., col 1, line 7+; col 2, line 34+; col 4, line 36+). The reference calls for lysing the cells and then filtering them. A preferred filtering material is diatomaceous earth (e.g., col 2, line 7-8; col 2, line 31+; col 4, line 36+). Colpan does not explicitly state that protein will be present in the lysate, however, the cell biologist of ordinary skill is aware that cells contain proteins. In addition, Colpan does not disclose reducing the amount of DNA and does not explicitly state that the amount of endotoxins will be reduced. Theodossiou discloses (e.g., page 182, table 5) that if a solution containing

DNA is filtered through diatomaceous earth, some reduction in the amount of DNA will occur. Theodossiou does not disclose a method which comprises reducing the amount of endotoxins.

The instant claims are drawn to a method for removing particles from a solution. There is no requirement that a protein ever be isolated, nor is there a lower limit on the amount of protein present (as long as a finite amount is present). There is also lower limit on the amount by which DNA or endotoxins are reduced. Thus, for example, one could begin with a solution which contains DNA at a concentration of 10 mg/liter, protein at a concentration of 2 micrograms per liter, and endotoxin at a level of 50 micrograms per liter, and after filtering, end up with a solution in which the amounts of DNA, protein and endotoxin are 9 mg/L, 1.9 μ g/L and 49 μ g/L, respectively. According to one embodiment of Colpan, cell lysis is followed by addition of 3M KOAc (e.g., col 4, line 6). This may have the effect of precipitating some of the protein. However, (a) some protein will remain in solution, and (b) other lysing methods are suggested (col 1, line 35) such as lysozyme and proteinase K. Thus, some protein would be present in the solution at the time of the filtration through diatomaceous earth. As for reducing the amount of endotoxins, neither reference provides specific instruction as to how to accomplish this. However, Colpan does disclose that the plasmid DNA should be further purified, using, e.g., ion exchange columns or

absorption/desorption ^{from} ~~form~~ mineral supports. The skilled chromatographer would have expected a reduction in the amount of endotoxins as a consequence of the purification process.

Thus, the claim is rendered obvious.

✦

[A copy of the "Theodossiou" reference has not been provided, as it was provided during prosecution of parent application 09/792789. In the event that applicants' counsel is unable to obtain a copy of this, a copy will be provided upon request]

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at (571)272-0562. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



**DAVID LUKTON, PH.D.
PRIMARY EXAMINER**